General

Guideline Title

Epidermal growth factor receptor (EGFR) targeted therapy in stage III and IV head and neck cancer.

Bibliographic Source(s)

Winquist E, Cripps C, Agbassi C, Messersmith H, Head and Neck Cancer Disease Site Group. Epidermal growth factor receptor (EGFR) targeted therapy in stage III and IV head and neck cancer. Toronto (ON): Cancer Care Ontario (CCO); 2011 Sep 30. Various p. (Evidence-based series; no. 5-12). [63 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Cripps C, Winquist E, Stys-Norman D, Devries M, Gilbert R, Head and Neck Cancer Disease Site Group. Epidermal growth factor receptor (EGFR) targeted therapy in stage III and IV head and neck cancer: guideline recommendations. Toronto (ON): Cancer Care Ontario (CCO); 2009 May 15. 32 p. (Evidence bases series; no. 5-12).

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

Recommendations

Major Recommendations

Locally Advanced Head and Neck Squamous Cell Carcinoma (HNSCC) (Stage III-IVB)

- Platinum-based chemoradiotherapy (CRT) is a recognized standard of care for the primary treatment of most patients with locally advanced HNSCC. 5-fluorouracil (5-FU) plus platin or monoplatin therapy appear most effective. In patients over age 70, the addition of platinum-based chemotherapy does not appear to provide an overall survival (OS) advantage compared to radiotherapy (RT) alone.
- The addition of cetuximab to intensified RT (concomitant boost or hyperfractionated schedule) may provide an alternative option to CRT. In one randomized controlled trial (RCT), this option demonstrated similar improvements in OS, progression-free survival (PFS), and time to local recurrence compared to RT alone.
- The role of anti-epidermal growth factor receptor (anti-EGFR) therapies in the treatment of locally advanced HNSCC is currently under study in large randomized trials, and patients with HNSCC should continue to be offered clinical trials of novel agents aimed at improving

outcomes.

Untreated Recurrent and/or Metastatic HNSCC

Cetuximab in combination with platinum-based combination chemotherapy is superior to chemotherapy alone in patients with recurrent and/or metastatic HNSCC, and is recommended to improve OS, PFS, and response rate in suitable patients.

Previously Treated or Unsuitable for Platinum-based Chemotherapy

Zalutumumab appears to be of benefit in patients with recurrent and/or metastatic HNSCC who are unsuitable for cisplatin-based chemotherapy or who have had disease progression despite treatment with cisplatin-based chemotherapy.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Locally advanced (nonmetastatic [stage III or IV]) or recurrent/metastatic head and neck squamous cell carcinoma (HNSCC)

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Oncology

Otolaryngology

Pharmacology

Intended Users

Physicians

Guideline Objective(s)

To evaluate the benefits associated with the use of anti-epidermal growth factor receptor (anti-EGFR) therapies in head and neck squamous cell carcinoma (HNSCC)

Target Population

Adult patients with locally advanced (nonmetastatic [stage III or IV]) or recurrent/metastatic head and neck squamous cell carcinoma (HNSCC)

Interventions and Practices Considered

1. Platinum-based chemoradiotherapy (CRT) (5-fluorouracil [5-FU] plus platin or monoplatin therapy)
2. Anti-epidermal growth factor receptor (anti-EGFR) therapy:
    - Cetuximab
    - Gefitinib
    - Lapatinib
    - Zalutumumab
    - Erlotinib
    - Panitumumab

Major Outcomes Considered

- Overall survival (OS)
- Progression-free survival (PFS)
- Quality of life (QoL)
- Tumour response rate and duration
- Toxicity associated with the use of anti-epidermal growth factor receptor (anti-EGFR) therapies

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Literature Search Strategy

In order to update the evidence identified in Section 2B in the original guideline document, the MEDLINE (2009 February through 2011 February week 1), EMBASE (2009 to 2011 week 6), and Cochrane Library databases (February 2011) were systematically searched for relevant articles, using the search strategy described in Appendix 1 in the original guideline document. In addition, the American Society of Clinical Oncology (ASCO) 2009 and 2010 online conference proceedings were searched for reports of new or ongoing trials. The reference lists from the relevant review articles were also searched for additional trials.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

- They were abstracts or full reports of randomized phase II or III trials of epidermal growth factor receptor (EGFR)-targeting monoclonal antibodies, either alone or in combination with radiotherapy (RT) or chemotherapy, versus a control therapy (including RT, chemotherapy, chemoradiotherapy, or best supportive care) in treatment of advanced head and neck squamous cell carcinoma (HNSCC)
- They reported at least one of the following outcomes: quality of life, toxicity, compliance, survival, time-to-progression, response duration, or response rate; or
- They were published reports of systematic reviews or evidence-based guidelines that addressed the guideline question

Exclusion Criteria

Articles published in languages other than English were excluded because of limited translation resources.

Number of Source Documents

The literature search update conducted in February 2011 yielded one meta-analysis and three new reports of the randomized controlled trials (RCTs) already included in the original document being retained for this update. Also, two out of 33 abstracts from the American Society of Clinical Oncology (ASCO) annual meeting proceedings contributed to the evidence base.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus (Committee)

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Synthesizing the Evidence

Based on an a priori assumption of between-study heterogeneity, a meta-analysis was not planned but will be done, if considered appropriate.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Methods

The Evidence-Based Series (EBS) guidelines developed by the Cancer Care Ontario Program in Evidence-based Care (CCO PEBC) use the methods of the Practice Guidelines Development Cycle. For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by two members of the PEBC Head and Neck Cancer Disease Site Group (DSG) and two methodologists.

Development and Internal Review

An updated Evidence-Based Series (EBS) report was initiated by the Head and Neck Cancer DSG of the CCO PEBC in 2011 and completed in 2011. The series is a convenient and up-to-date source of the best available evidence on epidermal growth factor receptor (EGFR) targeted therapy in head and neck cancer (stage III and IV). It was developed through systematic review, evidence synthesis, and input from practitioners in Ontario. The views and preferences of the target population were not sought for. The original systematic review has been retained in Section 2B of the new series, while new evidence from February 2009 to February 2011 is presented in Section 2A in the original guideline document. The updated Guideline Recommendations are presented in Section 1 in the original guideline document.

Disease Site Group Consensus Process

The members of the Head and Neck Cancer DSG reviewed the new evidence contained in Section 2A in the original guideline document via email.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Report Approval Panel (RAP)

Prior to the submission of this Evidence-Based Series (EBS) draft report for external review, the report was reviewed and approved by the Program in Evidence-Based Care (PEBC) RAP, which consists of three members: the PEBC director, the Head and Neck Disease Site Group (DSG) chair and an oncologist with expertise in methodological issues.

External Review by Ontario Clinicians

Following the approval of this EBS by the Head and Neck Cancer DSG members and PEBC RAP, the recommendations (see Section 1) and the evidentiary base (see Sections 2A and 2B) in the original guideline document were circulated to external reviewers in Ontario for their feedback.

Methods

The external review was conducted in two ways; by targeted peer review (TPR) and by professional consultation.

Targeted Peer Review

Seven targeted peer reviewers, from Ontario, Alberta, and Vancouver, considered to be clinical experts on the topic, were nominated by the authors. Three of the seven nominees accepted the invitation to be part of the TPR to review this EBS. On July 15th, 2011, the draft report and a five-scale questionnaire were sent to them via email. The questionnaire consists of nine items evaluating the method, results, and interpretative summary used to inform the draft recommendations. Comments from the reviewers are compiled below.

Professional Consultation

Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Medical and radiation oncologists and surgeons working in the field of head and neck cancer in Ontario were identified from the PEBC database and were contacted by email to inform them of the guideline and to solicit their feedback. Participants could participate using a Web survey tool or by hardcopy through regular mail or fax. They were provided with access to the questionnaire, the guideline recommendations (Section 1 in the original guideline document), and a link to the evidentiary base (Section 2 in the original guideline document). Participants were asked to rate the overall quality of the guideline (Section 1 in the original guideline document) and whether they would use and/or recommend it. Written comments were invited.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Head and Neck Cancer DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by randomized controlled trials, one meta-analysis and abstracts from the American Society of Clinical Oncology (ASCO) annual meeting proceedings.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- The addition of cetuximab to radiotherapy (RT) in patients with locally advanced head and neck squamous cell carcinoma (HNSCC) increased overall survival (OS) (median 49.0 months vs. 29.3 months; hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.57-0.97, p=0.03) and progression-free survival (PFS) (median 17.1 months vs. 12.4 months; HR 0.70, 95% CI 0.54-0.90, p=0.006) as compared with RT alone. Locoregional control (median 24.4 months vs. 14.9 months; HR 0.68, 95% CI 0.52-0.89, p=0.005) and objective response rate (74% vs. 64%; odds ratio [OR] for response 0.57, 95% CI 0.36-0.90, p=0.02) were also significantly improved.
- In one reported study, the addition of cetuximab to chemotherapy (cisplatin or carboplatin plus 5-fluorouracil) improved OS (10.1 months vs. 7.4 months, p=0.04), PFS (5.6 months vs. 3.3 months, p<0.001) and response rate (36% vs. 20%, p<0.001) compared to chemotherapy alone in patients with recurrent/metastatic HNSCC.
- In a small randomized trial, the addition of cetuximab to cisplatin improved the objective response rate (26% vs. 10%, p=0.03) but did not improve OS (9.2 months vs. 8.0 months, p=0.21) or PFS (4.2 months vs. 2.7 months, p=0.09), although the trial was inadequately powered to assess these outcomes.
- In one trial, PFS was shown to be significantly better in patient treated with zalutumumab than those on best supportive care (BSC) (HR, 0.63; 95% CI, 0.47 to 0.84; p=0.001). The improvement seen in OS (6.7 months versus 5.2 months) was not statistically significant (p=0.062). Zalutumumab was given in escalating doses until the patient developed a rash.

Potential Harms

- Cetuximab did not appear to increase common adverse effects that can occur during radiotherapy (RT). The most common and significant side effects (grades 3-5) of cetuximab were acneiform rash (17% vs. 1%, p<0.001) and infusion reaction (3% vs. 0%, p=0.01). Quality of life (QoL) was neither clearly improved nor worsened by the addition of cetuximab to RT.
- Hypomagnesemia was increased in patients receiving cetuximab in combination with cisplatin.
- Gefitinib was associated with an increased incidence of tumour hemorrhage as compared with weekly methotrexate (8.9% for 250mg/d and 11.4% for 500 mg/d vs. 1.9% for methotrexate).
- Concurrent chemotherapy is not only associated with additional adverse effects such as nausea, vomiting, and neutropenia but also with severe oropharyngeal mucositis in over 50% of patients. The latter represents a serious challenge to the quality of life, costs, and management of these patients.

Qualifying Statements

Qualifying Statements

- Chemoradiotherapy (CRT) is the current standard of care for many patients with locally advanced head and neck squamous cell carcinoma (HNSCC), and, to date, there is not adequate evidence for assessing comparisons of cetuximab plus radiotherapy (RT) to CRT or examining whether the addition of cetuximab to CRT is of benefit to these patients. However, there are six ongoing trials investigating the effect of the addition of epidermal growth factor receptor (EGFR) inhibitors, concurrently with, prior to, or following CRT, on overall survival (OS), progression-free survival (PFS), and time to local recurrence in these patients, which should determine whether cetuximab should be added to standard of care treatment.
- Postoperative CRT is also a standard of care for high-risk patients with HNSCC treated with primary surgery, and no evidence from randomized controlled trials (RCTs) is available to support the use of cetuximab plus RT in this setting.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the

report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2009 May 15 (revised 2011 Sep 30)

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Source(s) of Funding

The Program in Evidence-based Care (PEBC) is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Guideline Committee

Head and Neck Cancer Disease Site Group

Composition of Group That Authored the Guideline

For a current list of past and present members, please see the Cancer Care Ontario Web site .

Financial Disclosures/Conflicts of Interest

The authors declared that they have no competing interest.

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Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site .

Availability of Companion Documents

The following are available:

- Epidermal growth factor receptor (EGFR) targeted therapy in stage III and IV head and neck cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO); 2011 Sep 30. 7 p. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario (CCO) Web site .

- Program in Evidence-Based Care (PEBC) handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012. 14 p. Electronic copies: Available in PDF from the CCO Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on December 30, 2009. This NGC summary was updated by ECRI Institute on September 6, 2013.

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